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THE DUODENAL INHIBITION OF GASTRIC SECRETION

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The undersigned certify that they have read and recommend to the Faculty of Graduate Studies for acceptance a thesis entitled "The Duodenal Inhibition of Gastric Secretion", submitted by KENNETH LLOYD BOWES in partial fulfillment of the requirements for the degree of Master of Science.

ABSTRACT

The infusion of substances into isolated segments of small bowel has suggested two separate gastric inhibitory mechanisms of intestinal origin: (1) inhibition arising when the duodenal pH falls below 2.5 and (2) inhibition secondary to changes in osmolarity, arising from both the duodenum and the upper jejunum and probably dependent upon pancreatic and biliary secretions.

These studies are, however, of isolated pieces of intestine and do not necessarily reflect normal physiological events. This study was undertaken to evaluate these factors in the intact gut.

Gastric secretion was studied in Heidenhain pouch dogs subjected to successive transposition of the entire duodenum excluding the biliary and pancreatic ducts to the upper jejunum, mid-gut and terminal ileum.

There was a statistically significant increase in gastric secretion following transposition of the duodenum to the upper jejunum and a further significant increase after its transposition to the mid-intestine. Transposition of the duodenum from the mid-intestine to the terminal ileum had

no significant effect on gastric secretion. Moving the duodenum to the upper jejunum eliminates inhibitory mechanisms dependent upon acid chyme in the duodenum, whereas transposition to the mid-intestine must have removed other mechanisms, presumbly those secondary to changes in osmolarity.

These studies confirm the presence of acid and non-acid induced gastric inhibitory mechanisms of duodenal origin.

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TABLE OF CONTENTS

FIGURES

TABLES

TABLES

CHAPTER I

INTRODUCTION

The physiology of gastric secretion has been the subject of the majority of gastrointestinal research. In spite of this intensive study, many facets have yet to be fully explored. The role of the small bowel in the regulation of gastric acidity and in the development of peptic ulceration is one of these.

Our interest in this subject was aroused by the work of Martin's group in New York (101). They transposed the dog's duodenum to the terminal ileum and observed the development of antral and jejunal ulcers without an increase in gastric secretion. These results contradicted Brachney, Thal and Wangensteen's widely quoted experiment in which they saw marked gastric hypersecretion following either excision of the duodenum or its transposition to the mid-gut (13).

This experiment was undertaken in an attempt to resolve these differences and to clarify the role of intestinal factors in the regulation of gastric secretion. Dogs in whom Heidenhain pouches had been constructed were subjected to successive transposition of the entire duodenum to the upper jejunum, mid-gut and terminal ileum. Pouch secretion was studied in each of these stages. As the duodenal drainage of

bile and pacreatic juice was not altered, changes in hepatic and pancreatic function might accompany duodenal transposition. These were assessed with biochemical tests, enzyme substitution and post mortem examination.

The intestine is known to exert both inhibitory and stimulatory influences on gastric secretion, but the mechanisms and their importance is not yet clear. The pancreas and liver have been recently subjected to intensive investigation with some clarification of pathological, but not of physiological events. An understanding of the results of duodenal transposition must rest on an awareness of the work of others in this field.

INTESTINAL STIMULATION OF GASTRIC SECRETION

THE "INTESTINAL PHASE"

The first suggestion of an "intestinal phase" appeared in the work of Leconte (96), who introduced foodstuffs into the duodena of dogs and noted increased gastric secretion. Pavlov (126), however, was of the opinion that food in the duodenum exerted "either no effect or a very unimportant one".

The definitive proof of an intestinal gastric stimulatory role lies in the work of Ivy, Lim, and McCarthy (80). They constructed vagotomized total gastric pouches and reconstructed the gastrointestinal tract by esophago-duodenostomy

in dogs. When such a dog was fed, the stomach secreted after a long latent period, the maximal secretion occurring six hours after the meal.

Gregory and Ivy (57), found that transplanted fundic pouches would also respond, albeit very scantily, to such a stimulus indicating a humoral agent. Sircus (148) reported that distension of Thiry-Vella loops of duodenum and jejunum with water or dilute hydrochloric acid resulted in secretion from a dennervated pouch. Such an agent itself does not affect gastric secretion, so the effect must be hormonally mediated. Some investigators (117, 161) have been successful in preparing extracts from the small gut, especially the upper duodenum, which on intravenous injection stimulated gastric secretion.

Nervous Mechanisms

If a humoral mechanism exists, it is extremely difficult to evaluate the possible role of the nervous sytem. The only evidence suggesting neural involvement in the intestinal phase is the work of Ivy, Lim and McCarthy (80). They demonstrated inhibition of the intestinal phase with atropine in dogs with vagotomized pouches of the entire stomach.

Importance of Intestinal Stimulation

Beaumont (7), in his memorable studies of Alexis St.

Martin's stomach, noted "the gastric juice never appears to accumulate in the cavity of the stomach while fasting". Such a concept reflects the opinion of the majority today. Dragstedt (33) felt that it accounted for less than 10% of the gastric secretory response to a meal and that normally it was in abeyance. This was supported by the work of Griffon et al (61), who found that Heidenhain pouch dogs subjected to antrectomy underwent a 90% fall in gastric secretion.

Such studies are however not necessarily a good index of its normal physiological role. There is good evidence that the intestinal phase is potentiated by gastrin and vagal stimulation (58, 83). Thus, studies of it in isolation may give only a fraction of its true response. Day and Webster (27), felt that it was not important because of concomitant duodenal inhibition. Indeed, Griffon (61) found in his antrectomized dogs that gastric secretion increased by 50% following duodenectomy. Such a concept grows in importance when one recalls Shay's inability to demonstrate duodenal inhibition in duodenal ulcer patients (142).

INTESTINAL INHIBITION OF GASTRIC SECRETION

The duodenum receives the brunt of the stomach's enormous acid outflow and thus it is perhaps not unexpected that it should have some role in its production. Duodenal

inhibition is effected by acid or changes in osmolarity and results in depression of both gastric motility and secretion. These effects have been attributed to both nervous and hormonal mechanisms.

A. Acid Inhibition

Shemiakin (142), and Sokolov (153), were the first to report the inhibition of gastric secretion by the installation of acid into the dog's duodenum. Day and Webster (27), found acid to inhibit secretion secondary to sham feeding or the introduction of food into the intestine. Griffiths (62), and Shay (141), demonstrated it in humans. However, Ivy and McIlvain (81), Ivy, Lim and McCarthy (80), and Stevens (157), did not see inhibition with duodenal acid installation.

These differences were resolved by Pincus (128) in 1944 who studied gastric secretion in dogs with Pavlov pouches and duodenal fistulae. Inhibition was not seen above a duodenal pH of 2.5. Below 2.5 gastric secretion fell by 50%, and 100% inhibition was seen if the duodenal pH reached 2.0. Such inhibition he found to operate against food in the stomach or insulin. Since that time, acid inhibition has been extensively confirmed (2, 3, 4, 5, 26, 82, 95, 118, 149). Its effect against histamine induced secretion is however controversial.

Nervous or Hormonal?

The early investigators attributed acid inhibition to nervous mechanisms. Sircus (149) introduced acid into the duodenum just distal to the pylorus and saw significant inhibition in only innervated pouches. Code and Watkinson (26) found only slight inhibition of secretion by duodenal acid installation in Heidenhain pounches.

However, recently Jones and Harkins (82), Nanson (118), and Andersson (2, 3, 4, 5), have demonstrated very significant inhibition in Heidenhain pouches. Schapiro and Woodward (139), demonstrated acid and motility inhibition in patients with vagotomy, sympathectomy, splanchnicectomy, spinal cord section, at T_8 and T_9 and division of the intrinsic plexus, and concluded that it was not nervously mediated. The literature today appears to be leaning towards a hormonal mediation but it is by no means conclusive,

Physiological Significance

That acid-induced duodenal inhibition is an elicitable entity has been adequately demonstrated. However, such is not proof of a normal physiological mechanism. To demonstrate it in dogs one must infuse a minimum of 100 cc's and up to 400 cc's per hour of 0.1 N hydrochloric acid (2, 82, 118). With the added effect of dilution by food, it would seem unlikely

that duodenal acidity has much effect on gastric secretion. Thomas (159), studied the pH in the upper duodenum of dogs following a meat meal and found only 3 of 210 samples to be more acid than pH 3. These findings were confirmed by Humphreys (70).

These studies have left the significance of duodenal acid inhibition, at least in the normal course of events, in doubt. It should be noted however that Thomas (159) found the antral pH just prior to emptying to be 2.5. Thus, this mechanism might itself be the factor keeping duodenal pH at a higher level. Landor (95) stripped the stomach free of mucosa and observed a 300% increase in Heidenhain pouch secretion. The main effect of such a procedure would be to lower gastric acidity and remove pH based influences such as (a) gastrin release and (b) duodenal acid inhibition.

Studies in humans by Humphreys (70) and Thomas (159) have in general confirmed the rarity of truly low duodenal acidity. Such a mechanism might act as an emergency brake against occasional high levels of secretion such as those secondary to psychic stimulation which has not followed by food.

Clinical Significance

The patient with duodenal ulcer is obviously in need of

duodenal acid inhibition. Shay (141) was unable to demonstrate it, and postulated failure of this mechanism as an etiological factor. However, Hunt (71) did demonstrate it in 10 of 16 such patients. A clinical study of ulcer patients relating the degree of gastric acidity and the presence or absence of duodenal inhibition could prove interesting.

B. Non-Acid Induced Inhibition

A great variety of substances other than acid have been shown to inhibit gastric motility and secretion when introduced into the duodenum. These include fat, water, glucose, sucrose, pepsin and saline (54).

Ewald and Boas (41), and Pavlov and his pupils (126) demonstrated diminished secretion when fat was added to a dog's meal. Quigley, Zettleman and Ivy (133) noted that the effect was dependent upon fat reaching the duodenum. These results have been extensively confirmed (14, 43, 55, 80, 118).

Some of the above substances have been effective stimulants of acid secretion in studies on the intestinal phase. Sircus (149) has more clearly defined the properties of a substance producing inhibition. Normal saline he found to stimulate gastric secretion when infused into the duodenum. Hypertonic saline on the other hand had a marked inhibitory effect. The same held for solutions of fructose, sucrose and

glucose. In general, any substance increasing duodenal osmolarity above 274 milliosmols or lowering it below 50 milliosmols inhibited gastric secretion.

Nervous or Hormonal?

To effectively demonstrate a non-nervous mechanism, both the source of the proposed agent and its target organ must be dennervated. To date this has not been done. There are numerous studies (43, 131, 133), demonstrating inhibition in the dennervated Heidenhain and transplanted fundic pouch, but not one study has been made using a dennervated duodenum. It is felt today to be at least party hormonal by most investigators on the basis of:

1. Its demonstrations in transplanted pouches (43, 131, 133).

2. The intravenous administration of substances used to elicit it has no effect on gastric secretion (131, 149).

Role of Digestive Enzymes

Quigley and Meschan (131) in 1941 suggested that the products of fat digestion might be important in gastric inhibition, as fatty acids were more than two times as effective as neutral fats in inhibiting mobility. Sircus (149) was unable to demonstrate inhibition of secretion by the instillation of olive oil into the isolated duodenum unless it was

pre-mixed at 37° C for two hours with pancreatic juice. Menguy (105, 107, 108, 109, 113) demonstrated diminished duodenal fat inhibition in dogs and rats, whose bile ducts were diverted to the terminal ileum. In a comparative study of inhibition elicited by olive oil infusion into Thiry fistulae of the upper gut, he observed the following degrees of gastric secretory inhibition:

Olive Oil alone	2%
Olive Oil & Bile Salts	56%
Olive Oil & Bile Salts & Lipase	86%

The infusion of olive oil into the intact duodenum resulted in 88% inhibition. That the effect of pancreatic and biliary secretions might be partly due to a lowering of surface tension is suggested by Morgan's findings of increased inhibition when Tween 80 was added (115). Menguy however, could not demonstrate this mode and site of action (113).

Sircus (149) and Nanson (118), found fat induced duodenal inhibition to be effective against a meat gruel meal. Gregory (59) believes that it acts to prevent the release of gastrin for the following reasons:

1. Fat in the duodenum inhibits secretion induced by carbachol only in the presence of the antrum.

2. Secretion produced by perfusion of the antral pouch is inhibited by fat in the duodenum.

3. Intravenous gastrin's secretory effect is unaffected by the introduction of fat into the duodenum.

Such a concept leaves several facts unexplained:

1. Duodenectomy in antrectomized dogs results in a 45% increase in gastric secretion (61).

2. Gastric motility has been inhibited in antrectomized dogs with transplanted fundic pouches by the introduction of fat into the duodenum (the mechanism of motility inhibition is thought to be similar to secretory inhibition) (59).

3. The intraduodenal introduction of hypertonic saline solution was found by Sircus (149) to be effective against histamine induced secretion. Histamine acts by direct stimulation of the parietal cell.

C. Origin of Inhibitory Influences

Following a partial gastrectomy, the surgeon is frequently faced with the alternative of anastomising the stomach to either the duodenum or the upper jejunum. The site of origin of the inhibitory influences then assumes some practical importance. The vast majority of studies lack specificity however, speaking of the upper intestine or loops of duodenum and jejunum. Only one investigator, Sircus (149) has attempted to demonstrate acid inhibition in a site other than the

duodenum. On the basis of a small series of experiments he concluded that it could not be elicited from the upper jejunum.

Non-acid induced inhibition has been demonstrated to arise in the upper jejunum as well as the duodenum. Kosaka and Lim (92) noted inhibition of gastric secretion following the introduction of 40 cc's of olive oil into the colon. Similarly, Menguy (106) demonstrated it with the introduction of fat into the terminal ileum. It is difficult to accept these latter studies as demonstrating a physiological event.

D. Agents of Inhibition

The evidence reviewed indicates that hormonal agents are at least partly responsible for duodenal inhibition. Unlike the story of gastrin, the isolation and identification of these agents is still in its early stages. "Secretin" and "Enterogastrone" are currently the more popular of the proposed mediators.

Enterogastrone

The search for gastric secretion inhibitors in extracts of the upper gastro-intestinal tract has been very rewarding. Kosaka and Lim (92) prepared hydrochloric acids extracts from the mucosa of the small intestine which, when given intravenously or subcutaneously, inhibited gastric secretion. This

effect was lost by boiling the extract. Although none could be prepared from gastric mucosa, extracts of the descending and sigmoid colon were as effective as those from the upper small intestine. Lim later (97) found extracts of placenta, spleen, pituitary and adrenal to possess the same property.

Grey, Bradley and Ivy (49), found their extracts to be effective in the prevention of ulcers in Mann-Williamson dogs. More difficult to explain was their demonstration of a continuation of this protection after the therapy was stopped. When given thrice weekly to duodenal ulcer patients, they reported relief of symptoms within a few days and radiological regression in 2 months. As the inhibitory influence on gastric secretion was only of a few hours duration, they believed their extracts to act in some other way.

Other studies failed to confirm these findings. Grossman (64) could not prevent the development of histamine ulcers in dogs, and Morris et al (116) found it had no effect on the incidence of rumenal ulcers after pyloric ligation in rats. Subsequent studies in patients with duodenal ulcers have failed to demonstrate any benefit to duodenal ulcer patients (12).

Very little work has been done on enterogastrone recently. Obrink (121) has demonstrated that it has a nitrogen

content of 15%, but as pepsin or trypsin does not inactivate it, it is unlikely to be a protein. It is effective against histamine induced secretion without altering blood histamine levels. Its action follows a lag period of up to 45 minutes and lasts for up to 5 hours. Only volume secreted is diminished; acidity and chloride concentration do not change (121).

It is however unlikely that enterogastrone is the non-acid induced duodenal inhibitory hormone.

1. It is effective against a histamine stimulus whereas fat in the duodenum is not (59).

2. It has no inhibitory effect on gastric motility while fat in the duodenum is very effective (59).

3. Exogenous enterogastrone has no effect on gastric secretion in humans or rats while fat is a very effective inhibotor in rats (107).

4. It can be extracted from sites which bear little or no physiological relation to the stomach (92, 97).

Secretin

The new purified secretin preparations have been demonstrated to effectively inhibit gastric secretion (51, 65, 84). Such inhibition is present after pancreatic duct ligation (51), and pancreatectomy (89). Jordan (84) correlated the fall in gastric secretion with the rise in pancreatic

secretion.

It has been suggested that secretin is the mediator of acid induced duodenal inhibition (78). This, however, is unlikely as secretin release is at a much higher pH than that required for gastric secretion inhibition (54).

E. Interrelationships of the Duodenal Inhibition of Motility and Secretion

All substances which are known to inhibit gastric secretion also inhibit gastric motility. It has been assumed by most investigators that both actions are mediated in a similar manner. In regard to osmolarity, this appears to be true (72, 149). However, in regard to acid inhibition there appears to be a distinct difference. The Threshold of pH 2.5 has been shown to be necessary for secretory inhibition (128, 149). It is now generally accepted that acid inhibition of motility is effective at any pH below 6 (72, 73, 130). Hunt (72) postulates that the release of secretin at a pH of 6 results in elevated duodenal pH through its dual actions of inhibiting gastric emptying and stimulating alkaline pancreatic secretion.

The picture is complicated even more by Hunt's (73) demonstration that doubling the stomach's emptying time has the same effect on gastric acidity as doubling the secretion of acid.

PANCREAS

The early role assigned to the pancreas in the acid-ulcer axis was a simple one of neutralization. Thus, Mann and Williamson (99) produced ulcers in virtually all dogs whose duodenal secretions (pancreatic, biliary and duodenal) were drained to the terminal ileum. Similarly, the high incidence of stomach ulceration after gastro jejunostomy was attributed to the loss of the presence of alkali at the site of acid entry into the gut.

Such studies however involved numerous other factors, such as the loss of duodenal inhibition, which was not recognized at that time. Recently, interest in the role of the pancreas in gastric secretion has been stimulated by the recognition of fulminating peptic ulceration in association with pancreatic adenomas by Zollinger and Ellison (166). The pancreas is now known to influence gastric secretion by both exocrine and endocrine mechanisms.

Exocrine Function of the Pancreas and Gastric Secretion

1. Neutralization of Acid

The pancreatic secretions are highly alkaline and are believed to be important in the neutralization of acid. All procedures impairing the pancreas' exocrine function are

associated with an increased incidence of peptic ulceration (112, 135). Similarly, most experimental ulcer techniques are associated with a decreased pH of the site developing ulceration (165). However, great variations are seen in the incidence of ulcers following loss of pancreatic secretion and there are believed to be other factors operating. The exact role of acid neutralization alone has yet to be assessed.

2. Elaboration of Duodenal Inhibition

The probable importance of enzyme hydrolysis in the elicitation of duodenal non-acid inhibition has already been discussed. Numerous investigators (1, 19, 36, 38, 48, 68) have either prevented, diminished or reversed the hypersecretion seen after pancreatic duct ligation by the feeding of pancreatic extract.

3. Liver Disease

The liver's ability to detoxify secretagogues derived from the gastro-intestinal tract such as histamine has been ably demonstrated (8). Failure of the liver to detoxify or alternatively the production by the cirrhotic liver of a gastric secretagogue would profoundly affect gastric secretion. It has been suggested that influences of the pancreas on gastric secretion are mediated via liver disease produced by pancreatic insufficiency (109, 147).

Dragstedt (31) noted fatty livers in the majority of

pancreatectomized dogs. Pancreatic duct ligation or fistulae he found to produce little or no liver disease, and the feeding of pancreatic juice was ineffective in his hands in preventing it (31). Duct ligation and fistulization were found to result in liver disease by Elliott (38), Menguy (111), and Hein et al (68), but not by Devor (29), and Chey (19). Menguy correlated the onset of gastric hypersecretion after duct ligation with the appearance of abnormal liver function tests (97).

The studies of Ralli (134), Entenman (40), and Chaikoff (18), indicate that it is the absence of exocrine juice which results in a fatty liver. Duct ligation resulted in diminished lipid absorption and blood levels and increased hepatic lipid. Entenman (40) found that the addition of pancreas to the dogs' diet increased both lipid absorption and blood lipid levels. Chaikoff (18), found oral methionine to be effective in preventing fatty liver.

Endocrine Function of the Pancrease and Gastric Secretion

Although insulin has been known to be a potent stimulant of the vagal phase of gastric secretion for sometime, a physiological role of the endocrine pancreas in gastric secretion has only recently been postulated. Interest in this possibility was aroused by Zollinger and Ellison's description

of fulminating peptic ulcer disease in association with pancreatic tumors composed of non-insulin producing cells (166). The hypersecretion seen in these patients is attributed to a gastrin-like secretagogue which Gregory has extracted from both the primary and metastatic neoplasma (60). The possibility of these tumors being the overgrowth of cells normally involved in gastric secretion is suggested by Sircus (150), as:

1. 10% of these patients have diffuse islet cell hyperplasia rather than discrete tumors.

2. The adenoma cells are orderly and well differentiated and in this arrangement similar to the carcinoid, a tumour of normal endocrine cells whose clinical manifestations are a result of excessive serotonin production.

Glucagon

Zollinger and Ellison (166) postulated glucagon as the hormone involved since it is produced by the alpha cells and they found a substance having similar characteristics by electrophoresis and bio-assay in the serum of one of their patients. However, Clarke et al (24), Robinson et al (137) and Soloman and Spiro (154) found that glucagon in fact was an effective inhibitor. Hyperglycemia itself has a variable effect. At any rate, a physiological role for glucagon has yet to be

demonstrated.

Extracts of the Pancreas

Attempts to extract a secretagogue from the normal pancrease have generally failed (66, 140). However, Osborne (123) has extracted a bradykinen-like gastric secretagogue from the pancreata of 3 patients dying with duodenal ulcer, gastric ulcer and diverticulitis. Elliott (35) has been successful in obtaining a secretagogue from the atrophic dog pancrease produced by duct ligation. Atrophy of the dog pancreas secondary to ethionine is associated with hypersecretion. Partial atrophy has no effect on gastric secretion (94).

Pancreatectomy, Fistulae, Duct Ligation

The argument for a hormonal influence of the pancreas on gastric secretion is based on the effects of these procedures on gastric secretion and on the incidence of peptic ulceration. Both pancreatic fistulae and duct ligation increase and acid output of the stomach (31, 38, 92, 113). The degree of increase and the time of onset varies greatly with the investigator (19, 44, 52, 94, 103, 112). Pancreatectomy, on the other hand, appears to increase secretion only slightly (38).

Elliott believes duct ligation or fistula results in liberation of a hormonal secretagogue of pancreatic origin (35). As antrectomy markedly diminished the hypersecretion,

he feels a pancreatic-antral link to be involved. However, pancreatectomy has no effect on the hypersecretion produced by duct ligation (35).

LIVER

Exclusion of Bile

Exclusion of bile from the gut by duct ligation or fistulization results in gastric hypersecretion and ulceration in a high percentage of cases (9, 11, 67). As already mentioned, the neutralizing capacity of bile is negligible (112) and the ulcers seen are probably primarily due to hypersecretion. The role of bile in elicitation of intestinal inhibition would be abolished by these procedures (105, 107, 108, 113, 115). Heimberg and Hallenbeck (67) noted a rise in B.S.P. retention, increased liver lipid and increased response to intra-peritoneal but not intravenous histamine in these dogs, indicating that impairment of the histamine detoxification mechanism was also present. Knochet et al (90) noted hyponatremia, acidosis and hyperkalemia in biliary fistula dogs, changes which may in themselves result in hypersecretion (15, 37, 119, 143).

Cirrhosis and Portacaval Shunts

Farmer and Halsted (42) found a 17% incidence of peptic ulcers in the post mortem examination of 94 patients with

Laennec's cirrhosis as compared to a 10% incidence in the general autopsy population. Of 76 clinical bleeding cirrhotics, 18% were due to duodenal ulcer. These findings have in general been confirmed but there are still numerous dissenters and adequate control studies are lacking (23, 98, 125).

Experimentally, hypersecretion has been seen in dogs following portal ligation and after carbon tetrachloride induced hepatocellular damage (151). No association of hyperacidity and cirrhosis has on the other hand been found clinically (22, 124). Three mechanisms may be postulated to explain the experimental ulceration and hypersecretion.

1. Secretagogue produced by an ischaemic liver (151).

2. Failure of the liver either to remove a secretagogue from the circulation or to modify it to remove its effectiveness (75).

3. The elevated portal venous pressure may play a role (6).

The ischaemic liver's production of a secretagogue is unlikely as portacaval transposition in dogs results in as great a hypersecretion as does an Eck fistula (23, 145, 146). Elevated portal pressure is unlikely to be an important factor in ulceration, as shunts have no effect on the incidence of ulceration in cirrhosis (25) and in themselves have a high

experimental incidence of hypersecretion (25, 145).

Three substances produced by the gastro-intestinal tract have been suggested as the agents in cirrhosis which are liberated into the general circulation.

1. Gastrin

Gastrin was suggested as it is a well documented gastric secretagogue and decreased gastric motility with a resultant increased antral phase was seen by Reynall and Spray (136). However antrectomy has very little effect on the hypersecretion (25, 104, 145). Furthermore, gastrin does not appear to be modified by liver passage (47).

2. Ammonia

Ammonia, a potent secretagogue to the stomach, rises in the blood following a meat meal and has been suggested as the agent responsible for hypersecretion after portacaval shunts. However, the blood levels are never high and the peak blood concentration precedes the secretion peak by at least 2 hours (145). Colectomy which is reputed to lower ammonia production has no effect on gastric secretion (145).

3. Histamine

Histamine is the most popular of the suggested secretagogues. Irvine in several admirable papers (75, 76, 77)

demonstrated that the bacterial decarboxylation of histidine within the small gut produced a rise in urinary histamine which correlated temporally and quantitatively with gastric secretion produced by intra-intestinal administration of meat. After portacaval transposition, the introduction of histamine into the gut was much more effective as a secretagogue. The portal venous injection of histamine had a much smaller effect than the systemic injection (77). These results have been widely confirmed (8, 160, 162). Elevated post prandial blood histamine levels have been demonstrated by Day et al (28) and by Silen and Eisman (145). However, as Clarke (21) points out histamine cannot be the whole answer.

1. Fasting secretion after portacaval shunting is elevated whereas blood histamine levels do not change.

2. Atropine inhibits shunt hypersecretion but not that due to histamine.

3. Acid secretion secondary to antral irrigation is increased after shunting.

Site of Origin of the Secretagogue

Antrectomy, splenectomy, pancreatectomy and colectomy have no effect on shunt hypersecretion and thus by exclusion the small gut was seized upon as the likely source of the agent (104, 145, 146). Clarke et al (151) found that shunting of the

superior mesenteric vein alone produced hypersecretion, thus reinforcing this conclusion. However, Castaneda et al (16) have recently demonstrated that either iliectomy or jejunectomy alone have no effect on either established shunt hypersecretion or on the development of shunt hypersecretion. Both must be removed or the factors involved are much more complicated than the presence or absence of the small bowel.

THE INTESTINE AS A PHYSIOLOGICAL UNIT IN GASTRIC SECRETION

The preceding discussion has dealt with intestinal factors as if they were separate entities whereas all operate in conjunction at any one time. Experiments designed to evaluate intestinal factors as a whole are subject to difficulties in interpretation which are complicated by conflicting results.

In 1923 Mann and Williamson (99) reported a very high incidence of ulcers in dogs after removing the duodenum from its normal position and draining its secretions to the terminial ileum. These ulcers have been attributed to the loss of neutralizing juice (79), nutritional impairment (152), decreased mucosal resistance (45, 63, 100), and increased acid production secondary to impairment of duodenal inhibition (13), pancreatic and biliary fistulae (44, 38, 48, 53), liver disease (110, 111)

or increased intestinal phase (122). To a greater or lesser degree all are probably involved, but the exact role played by each is difficult to assess. Hypersecretion certainly does occur.

Brachney, Thal and Wangensteen (13) excised the duodenum and upper jejunum, re-anastomosed the bile and pancreatic ducts to the jejunum after gastro-jejunostomy and observed a rise in gastric secretion of 84% to 820% without the appearance of ulceration. The same authors translocated the duodenum and upper jejunum to the mid-gut and observed a rise in secretion of 113% to 364%. These results underline the importance of the duodenal inhibitory mechanisms, but are sharply contradicted by the work of Martin's group in New York (86, 87, 101, 122). These workers transposed a 10 cm. portion of the duodenum containing the bile and pancreatic ducts to the terminal ileum and observed the appearance of ulcers without the development of hypersecretion. When they placed the same segment in the mid-gut, only a small increase in acid secretion was observed and ulcers did not result.

On the other hand, Menguy and others have demonstrated that internal pancreatic and biliary fistulae either alone or together increased secretion and caused ulcers (110). Menguy believes that such hypersecretion is due to the concomittant

liver disease he has demonstrated.

That the intestine's stimulatory role is important is suggested by the work of Okinaka et al (122). When the duodenum was placed in the middle of the small intestine or terminal ileum, a later post prandial acid peak was noted than in normals with an Heidenhain pouch. Such a result suggests that duodenal stimulation is more important than antral! Other authors have not noted a later peak, but have seen a more gradually falling curve suggesting that duodenal inhibition is an important braking mechanism (141).

THIS EXPERIMENT

When physiological factors are studied in isolation, it is difficult to define their normal physiological role. Most of the work done on the role of factors distal to the pylorus has been of this type. Attempts to confirm the findings of such studies in a more physiological setting have led to conflicting results. Thus Wangensteen's duodenal excision or transposition experiments strongly confirm the presence of duodenal gastric inhibitor factors (13), whereas the work of Martin's group (86, 87, 101, 102) suggest that they do not exist. An interesting side-light of Martin's studies are his findings of ulceration without hypersecretion. Wangensteen, on the other hand, noted hypersecretion without ulceration and

by a remarkedly similar method. In our experiment we have attempted to reconcile these differences by proceeding in stages from Wangensteen's preparation to that of Martin while studying the effects on secretion and ulcer production.

The above two studies were performed in only a small number of dogs and were limited to what the effect of duodenal transposition was, rather than how it exerted its effect. We hoped to avoid these difficulties by using a larger number of animals, by moving the duodenum down the gut in smaller successive steps in the same animal and by the use of anciliary studies of such entities as plasma histamine, liver and pancreatic disease and correction of absorbtive defects with enzyme feedings.

To some extent, probably all research starts in one direction and ends in an entirely different setting. Our experiments were completed in the direction of our initial intent, but as the results became concrete we realized that other conclusions could be drawn from them, both as they stood and by the use of further studies on our original preparation. These include the separation in a physiological setting of acid and non-acid induced inhibition of duodenal origin, the relative importance of intestinal inhibition and stimulation of gastric secretion, the time of action of duodenal

inhibition, the role of pancreatic exocrine factors in the intestinal inhibition of gastric secretion and the role of malabsorption in the experimental production of peptic ulcer.

CHAPTER II

METHODS

GENERAL OUTLINE

Gastric secretion was studied in dogs with Heidenhain pouches before and after transposition of the entire duodenum to the upper jejunum, mid-gut, and terminal ileum. For ease of discussion, the various preparations have been designated as H-pouch, Stage I, Stage II, and Stage III, where each term stands for the following preparation:

H-pouch: A normal dog with a Heidenhain pouch.

Stage I: The entire duodenum was moved one foot down the gut, with restoration of gastro-intestinal continuity by gastro-jejunal and jejuno-duodenal end to end anastomosis.

Stage II: The duodenum was moved from the Stage I position to the mid-point of the small gut.

Stage III: The duodenum was moved to the terminal ileum within thirty inches of the ileocecal valve.

In the original plan each dog was to undergo successive transposition through each of the above locations (figure 1). A high mortality rate in the mid-gut to terminal ileum operations necessitated bringing some dogs directly to the mid-gut,

studying their secretion and then transferring their duodena to the terminal ileum. A third group of dogs was studied in terms of hourly gastric secretion following a standard meal as both Heidenhain pouch preparations and after transposition to the terminal ileum.

In addition to gastric secretion, the following laboratory determinations were made at each stage of the experiment:

B.S.P. retention

serum alkaline phosphatase

serum amylase

plasma histamine

Controls

To rule out the effect of operative trauma, and to determine the reversibility of the changes noted, gastric secretory studies were made before and after

1. Conversion of a Stage I to a H-pouch preparation
2. Conversion of a Stage II to a Stage I preparation
3. Conversion of a Stage III to a Stage I preparation

Pancreatic Substitution Therapy

Pancreatic substitution therapy was carried out in two normal dogs and in two Stage III dogs. The effect of this treatment on gastric secretion was studied.

SPECIFIC DETAILS OF METHODS

Experimental Animals

Mongrel dogs supplied by the Vivarium of the University of Alberta were used exclusively. Although most were predominantly of a Labrador strain, a great variety of breeds were used. Prior to use, each animal was quarantined for two weeks to rule out infectious disease, debarked, dewormed with a vermifuge specific for tapeworms, and vaccinated against infectious canine hepatitis and distemper. Any pathology found was promptly treated prior to introduction of the animal into the study.

General Care

While on collections, the dogs' conditions with reference to sores, eating, hydration and activity were recorded daily. Each dog was weighed weekly and when not on collections examined twice every week. Acid erosions about the cannula were treated by diversion of acid juice with a catheter or bag and local application of an inert powder. Abscesses about the cannula were drained as required.

Feeding

Each dog received four meals a day at 9.30 a.m., 11.30 a.m., 1.30 p.m., and 3.30 p.m., of a semisolid mixture of food

designed to maintain the best nutritional state possible.

Pancreatic Enzyme Therapy

The effect of pre-digestion of a meal on Heidenhain pouch secretion was studied in both normal and Stage III dogs. To a standard meal twenty grams of Viokase was added. This was then thoroughly mixed for three hours at 37°C and then fed to the animals in the study. The amount of food fed was constant before and during the substitution therapy which was continued for sixty days. The secretion of two normal dogs was also studied during the feeding of food mixed and heated as above, but without the addition of Viokase.

Collections of Gastric Juice

Collections were made into a Bard urinal bag which facilitated removal at frequent intervals. A minimum of eight collections was made in every dog at each stage of the experiment. Four types of collections were utilized, but the same type of collection was used in each dog throughout the experiment.

1. Twenty-four hour, four meal collection:

After a sixteen hour fast, the bag was placed on the dog's cannula and the first of four meals of standard food was given. Three further meals were offered during the day. Each evening the bags were emptied to prevent excessive weight

on the pouch. The night secretion was collected in the morning at the same time as the collection began, and the two samples pooled. Water was allowed as desired during the collection.

2. Eight hour, hourly post-prandial collection:

After a sixteen hour fast, each dog was fed twelve ounces of the standard meat gruel meal, and simultaneously a bag was attached to the H-pouch cannula. Collections were made hourly into individual test tubes for eight hours. Water was not given during the collections. In the early experiments a fasting collection for 1 hour prior to feeding was carried out, but as acidity in any such specimen was negligible, these were discontinued. Certain dogs would damage their pouch overnight and 24 hour collections could not be done. This type of collection was then used, the hourly acid out-put being totalled for a total eight hour post-prandial value.

3. 24 hour, hourly post-prandial collection:

After a 16 hour fast each dog was fed as in #2 and hourly collections were made. The period of collection was prolonged for 24 hours, but otherwise conditions were identical to the eight hour hourly post-prandial collections. Water was withheld.

4. Six hour post-prandial collection:

In Stage III dogs, difficulty was encountered in providing the same stimulus as in earlier studies due to anorexia. Therefore this type of collection was devised and used for dogs both prior to entrance into Stage III and after Stage III surgery. Fasting conditions were established as above and then simultaneous feeding of 12 ozs. of the standard meal and application of the Bard urinal were carried out. Secretion was collected for six hours. No water was allowed.

All types of collection were discontinued when:

1. A dog did not eat within 30 minutes of feeding or in the case of the twenty four hour, four meal collections, if food was left in the dish after 4.30 p.m.
2. Vomiting or retching occurred.
3. Coprophagy occurred.
4. Tears in the pouch were detected.

Twenty four hour, 4 meal collections and total six hour post-prandial collections were carried out in the vivarium under normal conditions of activity. All hourly collections were carried out in the Surgical Medical Research Laboratories. As the Pavlov stand which has classically been used for gastric secretory studies was very tiring, its use was discontinued. Instead, collections were made in the standing position after pressure on the abdoman to ensure emptying of the Heiderhain pouch.

Laboratory Procedure

1. Determination of gastric acidity

Gastric juice was thoroughly stirred and a sample titrated with sodium hydroxide to an end point with Topfers reagent. All results were expressed in terms of total mEq free hydrochloric acid secreted.

2. B.S.P. Determination

After sixteen hours of fasting, 5 mg/Kg of B.S.P. dye was injected intravenously. Thirty minutes later blood was drawn from a different limb and dye concentration determined according to the method of Ingleffinger and Bradley (74).

3. Alkaline Phosphatase

This was determined on freshly drawn blood by the method of Sommer (155).

4. Serum Anylase

Anylase was determined by the method of Somogy (156).

5. Plasma Histamine

This was determined according to the method of Shore et al (144).

6. Serum Electrolytes

Serum sodium, potassium and chloride were determined by a flame photometer whenever a dog's hydration or nutritional status was poor. Such studies were used to direct therapy

only, and are not included in this thesis.

Surgery

Pre-operative and Post-operative care

All dogs were fasted for twenty-four hours and deprived of water for sixteen hours prior to surgery. Anaesthesia was attained with 0.5 cc/kg. nembutal administered intravenously. Hydration was maintained on the day of surgery and on the first and second post-operative day by means of 30 cc/kg. 5% dextrose saline given either intravenously or subcutaneously. After the second post-operative day, water and then milk and pablum were given as tolerated. By the fourth post-operative day, most dogs were able to tolerate the normal feeding regimen.

Incision

All operations were performed through a midline upper abdominal incision extending from the xiphoid process to or just below the umbilicus. Strict asepsis was maintained at all times.

Heidenhain Pouch Construction

A point on the greater curvature of the stomach, just medial to the most medial short gastric artery, was selected and the marginal artery divided and ligated. Two clamps were placed into the omental gap such that their upper ends were

as close to the left side of the esophagus on the fundus of the stomach as possible. The stomach was then divided between the clamps. A running haemostatic locked chromic suture was used to close the stomach and pouch and the clamps were then removed. A second running sero-muscular Connel suture of 2-0 chromic was placed over the first suture to bury the suture lines. Prior to closure of the pouch, a cannula was inserted. The cannula was led through the anterior wall of the pouch and thence through the lateral abdominal wall. Omentum was then sutured about the cannula.

Stage I Duodenal Transposition

Just distal to the pylorus, as recognized by palpation and the location of the veins of Mayo, the duodenum was divided between clamps. The ligament of Treitz was then identified and divided until the duodeno-jejunal junction could be brought forward into the wound. Transection between clamps was carried out at the site where Treitz ligament had been attached. The duodenum was then put to one side and the jejunum brought up to the pylorus and anastomosed in an end to end manner to the stomach. A point on the jejunum one foot below the pylorus was then selected. The jejunum was divided between clamps at this site and the ends anastomosed iso-peristalitically to the extremities of the duodenum.

Stage II Duodenal Transposition

Upon reopening the abdomen numerous adhesions were always seen. Division of these was necessary both to identify the duodenum and to facilitate moving it distally. After the upper and lower jejuno-duodenal anastomosis' were identified, the gut was divided between clamps at the site of the anastomosis, care being taken to include all the druodenum in the duodenal segment. The jejunal continuity was re-established by end to end anastomosis of the jejunal arms. The small gut was then carefully measured in hands and the mid-point found. The division of the gut at this point and re-anastomosis to include duodenum was carried out in a manner similar to that of the Stage I procedure. Post-mortem examination confirmed the position of Stage II transposition to be truly mid-intestinal.

Stage III Duodenal Transposition

Adhesions were now prominent and their division and the location of the duodenum frequently took up the greater part of the operating time. One of two alternate procedures was then used.

1. The duodenum was freed from the mid-gut at the suture lines as in Stage II.
2. The lower end of the duodenum was divided at the suture

line. Transection at the upper end was however in the mid-gut about 3" or 4" above the duodenum and above the lowest marginal artery. Considerable difficulty with anastomotic leaks encountered at the upper anastomosis prior to the adaption of this procedure. After one or the other of these procedures, the terminal ileum was divided within thirty inches of the ileocecal value and the ends brought up and anastomosed iso-paristoltically to the duodenum similar to the procedure described in Stage I.

Post-operative closure after all procedures was by means of interrupted O chromic on the linea alba and running 2-O chromic for the subcutaneous payers. Either subcuticular running chromic or interrupted mattress silk was used on the skin.

Collections were commenced 3 weeks after pouch surgery and 2 weeks after the other operations.

AUTOPSIES

A thorough abdominal post mortem was carried out on all dogs after death, and if the cause of death was not found the chest was opened. The stomach and the entire small intestine was opened and carefully inspected. The position of the various stages of transposition was carefully noted. Sections were taken of the liver, pancreas, duodenum,

gastro-jejunal anastomosis, antrum, fundus, pouch, kidney and adrenal and examined microscopically.

CHAPTER III

RESULTS

I. GASTRIC SECRETION

1. The Effects of Transposing the Duodenum to Various Levels of The Small Intestine

Stage I - Transposition

When one foot of jejunum was interposed between the stomach and the duodenum, gastric free acid output rose in 13 of 16 dogs, with a net average increase of 38%. (Table I). The three dogs whose secretion failed to rise and the one (344) who demonstrated only a 5% increase had several features in common which were not seen in the other dogs. All had a prolonged period of convalescence (up to 2½ months) following Stage I surgery marked by anorexia, weight loss and recurrent vomiting. It is difficult to define the exact relationship of these clinical findings to secretion as no collections were made while they were present.

Stage II Transposition

Thirteen dogs successfully underwent duodenal transposition from the Stage I position to the mid-gut. Twelve of these increased their Heidenhain pouch acid output for a net average increase of 73% (Table II). If the Stage II secretion

is compared with that obtained in the same animals as Heidenhain pouch preparations, a net average increase of 133% is seen. (Table III). No reason could be found for the failure of #314 to demonstrate an increase in secretion while he was a Stage II preparation. He died ten days after Stage III transposition with gross ascites and congestive heart failure. The autopsy failed to demonstrate any other abnormality.

Stage III Transposition

The high mortality rate of surgery, the short survival time of the preparation itself, and the failure of many dogs to eat drastically reduced the number of dogs in this group suitable for study. All four of those whose secretion could be compared to Heidenhain pouch levels demonstrated an increase averaging +151% (Table IV). The closer the duodenum lay to the terminal ileum, the smaller was the increase. This is probably related to the physical condition of these animals. However, only two of the four suitable for study in both Stage II and Stage III demonstrated increased secretion (Table V).

Table VI summarizes the results given in Tables I to V.

Controls

Four dogs were studied before and after moving the duodenum from a relatively distal position in the small intestine to one closer to the stomach. Three of the four

demonstrated a fall in Heidenhain pouch secretion (Table VII). These were not absolute controls in that these animals were not returned to their original status for comparison. They were done to demonstrate that the surgery itself did not produce an increase in secretion, and that the increases in secretion could be reversed.

2. The Pattern of Gastric Secretory Response in the Presence and Absence of the Duodenum

Five dogs underwent hourly collections for 24 hours following a standard meat gruel meal both prior to and after transposition of the duodenum to the terminal ileum (Stage III).

(a) Hour of Maximum Secretion

The peak hour of gastric secretory response in a Heidenhain pouch preparation varied from 1 to 6 hours. Following Stage III transposition no consistent change was noted in the peak hour of secretion in the group studied (Table VIII).

(b) Late Response

Gastric secretion fell to 10% of the maximum response by 7 to 14 hours after the test meal. This response did not change consistently following duodenal transposition (Table IX).

(c) Time Relationships of Duodenal Inhibition

The 24 hour collection period was divided into 4 phases

and the average secretion in each phase before transposition compared to that seen after transposition. Each phase was named according to the stimulus most likely to be responsible for the major portion of the secretion.

Antral phase	hour 1-4 after feeding
Antral and Early Intestinal phase	hour 5-8 after feeding
Intestinal phase	hour 9-16 after feeding
Fasting phase	hour 17-24 after feeding

Table X summarizes the percentage change in each of these phases after duodenal transposition to the terminal ileum. All phases of secretion were increased. Superficially it appears that the maximal increase is in the late stages. However, the method of collection is such that when small volumes are concerned, as in the late response, gross inaccuracies may be seen. Thus, as quantities of secretion below 1 cc. are not measurable in terms of acidity, it is possible that 0.160 mEq HCL might be produced and recorded as zero. An increase in volume with no change in acidity could result in very impressive percentage increases on paper. Whether the tremendous increases seen in the late responses can be accounted for solely on this basis is debatable.

3. The Effect of Pancreatic Substitution Therapy on Gastric Secretion

Normal Animals

The incubation and mixing of food for 3 hours at 37° C had no effect on H-pouch secretion. When Viokase was added a 28% increase in gastric secretion was noted immediately and this persisted for the sixty days of the study. (Table XI).

Stage III Animals

Two Stage III dogs were studied for 62 and 15 days respectively. The shorter period in #462 was due to his death from leakage of acid from around the cannula into the abdomen. No change was noted in acid output either in the early or late stages of Viokase feeding (Table XI).

II. BIOCHEMICAL STUDIES

1. Liver Function

Serum Alkaline Phosphatase and B.S.P. retention remained within normal limits in all dogs throughout the experiment (Tables XII and XIII).

2. Serum Amylase

Great variation was noted in both normal and experimental animals. No significant change was noted after duodenal transposition in any animal. (Table XIV).

3. Plasma Histamine

In general, experimental animals had slightly lower fasting and 3 hour post prandial levels than normals. However, the number of determinations is not sufficient on which to base any conclusion on the validity of this fall. (Table XV)

III. CLINCIAL AND PATHOLOGICAL CHANGES FOLLOWING DUODENAL TRANSPOSITION

1. H-pouch Preparation

Following construction of a Heidenhain pouch all dogs lost an average of 13% of their body weight (Table XVI). In spite of this activity, appetite and general appearance were normal. Viokase was fed to 2 Heidenhain pouch dogs and resulted in a return to preoperative weight levels. (Table XVII). Post-mortems on this group failed to demonstrate any abnormalities.

2. Stage I Transposition

By the second post-operative week, all but four of these animals had regained their pre-operative degree of activity appetite and weight. These four failed to demonstrate gastric hypersecretion and have already been referred to. Liver biopsies at the time of Stage II surgery were normal in all dogs. For the group, there was a small net average weight gain. (Table XVI).

3. Stage II Duodenal Transposition

A net average weight loss of 10% or 1% per week was seen in this group. (Table XVI). Except for this and the occasional loose stool, most animals were in good general condition throughout their tenure as Stage II preparations. However, four dogs did die of the following causes:

#313 Lung Abscess

#315 Intussusception

#337 Perforation of one of five subacute jejunal ulcers

#344 Sacrificed because of inanition. At autopsy only adenomatous proliferation of glandular tissue at the gastro-jejunal anastomosis was noted (Figure II). There were no other findings.

Five animals died in the immediate post-operative period following attempted Stage III transposition of anastomotic leaks, intussception, volvulus and evisceration. Post mortems on all these animals failed to reveal any degree of hepatic, pancreatic, renal, or gastrointestinal pathology other than that immediately responsible for their deaths.

The dog who failed to demonstrate hypersecretion after Stage II surgery (#314) has an interesting terminal history. Five days after Stage III transposition he was given a blood transfusion and the next day massive ascites developed. In

spite of diuretics, he died five days later. The post mortem findings were those of congestive heart failure but in addition some loss of liver glycogen was evident.

4. Stage III Duodenal Transposition

Twleve dogs survived the immediate post-operative period following Stage III transposition. All developed full blown malabsorption syndromes marked by marked weight loss (net average of 28% or 4.5% per week) and frequent foul smelling and watery stools (Table XVI). After two to three weeks those animals who eventually survived the longest began to hold their weight steady and pass less frequent and more normal stools. The clinical state of an animal was closely related to the amount of intestine below the duodenum. Two animals were fed pancreatic extract with significant improvement in their condition (Table XVII).

Although Serum Alkaline Phosphatase and B.S.P. determinations were normal in all dogs liver disease was seen microscopically in three dogs (Figures 3, 4, 5). No correlation can be drawn between liver disease and gastric secretion (Table XVIII).

Peptic Ulceration

A good comparison between degree of hypersecretion and the development of ulcers cannot be made as in three of the

four dogs developing ulcers the conditions necessary for acceptance of the gastric secretory studies were not met. It is interesting to note, however, that the one whose secretory studies were acceptable did not differ greatly from other dogs in the same position (Table XIX).

CHAPTER IV

DISCUSSION AND CONCLUSIONS

A statistically significant rise in gastric secretion has been demonstrated following successive transposition of the duodenum and bile and pancreatic ducts to the upper jejunum and then to the mid-gut. Transposing the duodenum from the mid-gut to the terminal ileum failed to produce any significant change in gastric secretion in the small number of animals studied. The difference between the hypersecretion of Stage II and Stage III over H-pouch levels is small and the hypersecretion seen in Stage III animals may thus be attributed largely to the same mechanisms responsible for the hypersecretion of Stage II. What is the explanation for these findings? The more likely possibilities will be considered in turn.

1. Liver Disease

In the presence of significant liver disease, gastric hypersecretion and peptic ulceration have been demonstrated experimentally (9, 11, 91, 133, 144). Such an increase has been attributed to the escape of histamine into the general circulation (77).

The only animals demonstrating any evidence of hepatic

disease were three Stage III dogs, whose livers on microscopic section were pathological. Gastric secretion studies were acceptable in two of these. There was no correlation seen between the development of liver disease and the levels of secretion. One of these dogs demonstrated an increase of Stage III over Stage II and one did not. (Table XVIII).

The increases seen after Stage I and Stage II duodenal transposition cannot be attributed to hepatic disease as laboratory and histological investigation revealed normal livers. Supporting this conclusion are the normal plasma histamine levels seen in these dogs.

2. Pancreatic Disease

In addition to the loss of pancreatic secretion, duodenal transposition might impair pancreatic function through accidental injury of the ducts or direct trauma to the gland. Pancreatic duct ligation, pancreatitis and pancreatic fistulae increase gastric secretion (38, 102). Significant duct injury was ruled out by microscopic studies of the pancreata of all dogs at autopsy. The serum amylase levels were universally elevated in Heidenhain pouch and duodenal transposition dogs, but the latter did not show any higher levels than the former.

Loss of pancreatic enzymes from the gut is probably

not an important factor, as their replacement with viokase therapy had no effect on the hypersecretion of Stage III dogs in spite of a very significant improvement in general condition.

3. Malnutrition

This feature appears to be common to many experimental ulcer producing procedures. It is probably not a significant factor in this experiment for the following reasons:

1. The severe malnutrition seen in Stage III animals did not correlate with the levels of secretion seen in Stage III as compared with Stage II.

2. Stage I transposition resulted in an increase in secretion in the face of excellent nutrition.

3. Pancreatic enzyme therapy, although having a marked beneficial effect on the general condition of Stage III animals did not affect the hypersecretion.

4. Elaboration of a Gastric Stimulatory Influence by the Small Intestine

Duodenal Transposition effects four major changes in the small intestine.

1. Exposure of the jejunum to a more acid pH.

2. Removal of digestive enzymes from the upper intestine.

3. Introduction of digestive enzymes and fluid at a lower level in the small intestine.

4. Changes in intestinal motility.

(1) Exposure of the Jejunum to a More Acid pH.

It seems unlikely that an acid stimulus to the jejunum would result in the stimulation of a physiological mechanism stimulating gastric secretion. It is possible that jejunum inflammation might result in the production of an abnormal substance which affected gastric secretion. Histamine, a potent gastric secretagogue is involved in inflammatory processes, but it cannot be the agent responsible in these studies as the livers were normal and elevations in plasma histamine levels were not seen.

(2) Removal of Digestive Enzymes from the Upper Intestine.

There is no evidence that digestion plays any role in the intestinal stimulation of gastric secretion.

(3) Introduction of Digestive Enzymes at a Lower Level in the Small Intestine.

It might be postulated that the introduction of the large volumes of pancreatic and bile secretions into the lower intestine would result in an increased intestinal phase. The late post prandial gastric secretory response would be primarily affected by this. This would not explain the increased

secretion seen early in the post prandial period.

(4) Changes in Intestinal Motility.

This would be equally affected by moving the intestine proximally from a distal position. However, this resulted in either no change, or a fall in gastric secretion. Post mortem examination revealed significant dilatation above an anastomosis in only one dog (#461 - gastro-jejunal anastomosis), and his gastric secretory studies did not differ from other animals in his group.

5. Loss of Inhibitory Influences

The intestine is believed to be capable of inhibiting gastric secretion by two apparently independent mechanisms.

1. Acid induced inhibition arising solely in the duodenum (106, 149).
2. Non-acid induced inhibition arising throughout the small intestine and dependent upon enzymatic splitting of food stuffs (106, 149).

The author believes that the changes in gastric secretion can be explained on the basis of loss of these mechanisms.

Stage I Duodenal Transposition

Menguy (106) and Sircus (149) maintain that acid results in inhibition of gastric secretion only when it is

infused into the duodenum. A duodenal pH below 2.5 is necessary for such inhibition (129), and this is seen only rarely in the dog's duodenum (159, 70). Placing twelve inches of jejunum above the duodenum is likely to significantly raise the duodenal pH by (a) absorption and (b) dilution and neutralization by jejunal succus entericus, and reflux of neutrallizing pancreatic juices which would act to buffer acid before it reached the duodenum. Stage I transposition would then remove at least a great part of acid induced inhibition, resulting in a rise in gastric secretion. Non-acid induced inhibition arising in the duodenum or jejunum would not be altered as enzymatically split substances would still be present at jejunal and duodenal surfaces.

Stage II Transposition

Placing the duodenum in the mid-intestine has two major influences on non-acid induced inhibition.

(1) It removes the enzymes which might be necessary for the elicitation of this type of inhibition. Although they would still be produced, their influence would be at a time when the stomach was no longer secreting at high rates and their influence would then be less.

(2) It removes the duodenal mucosa as a source of non-acid induced inhibition when it could act against high rates of

secretion.

As Viokase did not diminish the hypersecretion of Stage III animals, the major effect of transposition could not be the loss of pancreatic enzymes and the importance of bile and the duodenal mucosa itself are underlined.

The duodenal mucosa may be the source of an inhibitor substance which must be absorbed from the intestine distal to the duodenum. Stage II transposition may by-pass the site of absorption or if it is absorbed throughout the small bowel, it may not leave enough bowel for effective absorption. Alternatively the duodenal mucosa cells may produce a substance and liberate it directly into the blood stream upon appropriate stimulation.

Stage III Transposition

If the hypersecretion is due to loss of a duodenal inhibitor factor liberated directly into the blood stream, no significant further increase in gastric secretion should be seen in dogs converted from a Stage II to a Stage III preparation. It is possible that a small increase could be seen due to the withdrawal of inhibitory influences acting late in the post-prandial gastric response upon small quantities of secretion. If absorption of the inhibitor is important, a significant elevation in secretion could be expected upon conversion

of a Stage II to a Stage III preparation. In a small number of dogs only a slight increase was seen. By comparing the elevation above H-pouch levels of Stage II and Stage III preparations the validity of this may be checked. Stage II animals averaged 133% hypersecretion, and Stage II animals averaged 151% hypersecretion. This difference is small.

The gastric hypersecretion produced by duodenal transposition is then attributed by the author to the successive loss of two independent gastric secretion inhibitors of duodenal origin. Acid-induced inhibition would appear to be the least important of the two. Duodenal inhibition triggered by a some non-acid stimulus is responsible for the majority of the duodenum's inhibitory influence and probably is the result of the direct release into the blood stream of a substance produced by the duodenal mucosa. We were unable to confirm the dependence of non-acid induced inhibition on pancreatic secretion. This study is the first confirmation in the intact gut of the existence of two independent gastric inhibitor factors of duodenal origin.

Integration of Duodenal Inhibition and Stimulatory Influences

Martin's group reported a later post-prandial peak of gastric secretion following duodenal transposition (122). Other workers have not noted this, but have seen a more gradual

fall in gastric secretion following removal of the duodenum prompting reference to the duodenum as a "brake" on gastric secretion. Shay postulated that the high night secretion of duodenal ulcer patients could be explained on the basis of deficiency of duodenal inhibition (141).

Our 24 hour, hourly collections before and after transposing the duodenum were prompted by these results. An increase in "antral, intestinal and fasting" phases was seen in all dogs. We were unable to confirm Martin's results; nor were we able to demonstrate a more gradually falling curve after removal of duodenal inhibition. Duodenal inhibition appears to exert its influences on all phases studied in this experiment. No observations on the relative importance of its inhibition against antral, intestinal or fasting secretion could be made in this study.

The Experimental Production of Peptic Ulceration

Four dogs developed peptic ulceration during the course of this experiment. Three of the four were Stage III preparations. As no significant difference in secretion was seen between Stage II and Stage III, some factor other than hypersecretion may be involved. However, secretion studies were not acceptable in any of the Stage III dogs who developed ulcers and whether their acid production was mirrored by the

dog's studied cannot be determined. Further studies of hypersecretion and ulceration in Stage III animals could prove interesting.

Questions Arising From the Results of Duodenal Transposition

There are numerous factors yet unexplained in the intestine's influences on gastric secretion. The exact site of origin of these influences is unknown. This study underlined the role of the duodenum. A similar method might be utilized in the study of other segments of the small intesting.

As the increases seen were demonstrated in Heidenhain pouches, the factors removed must have been largely humoral. Most authors feel that they are in fact hormonal. Definitive proof of this must await the successful preparation of the dennervated duodenum, which no doubt will prove technically extremely difficult.

This thesis favours the liberation of an agent from the duodenal mucosa as the mode of duodenal inhibition. The alternative possibility that absorption from the gut is important may be tested by studying gastric secretion following resection of varying portions of the jejunum and ileum.

To the clinician, more important than any of the above would be the confirmation of the relative importance of acid and non-acid gastric inhibitors of intestinal origin in man.

Patients with both intestinal fortitude and gastro-intestinal fistulae would be required for such studies. Of equal clinical interest is Shay's still not unproven theory that duodenal ulcer patients lack the ability to inhibit gastric secretion when duodenal pH falls to low levels.

Physiological Significance of the Results of Duodenal Transposition

If the hypothesis advanced as explanation for the results of duodenal transposition is correct certain important conclusions may be drawn.

(1) The duodenum's net effect on gastric secretion is inhibitory and is mediated by both acid and non-acid induced mechanisms. This confirms the physiological importance of these factors which until now have been demonstrated only in studies on the isolated duodenum.

(2) Inhibition induced by an acid pH appears to be responsible for only one third of intestinal inhibition while that secondary to a non-acid stimulus appears to be responsible for two thirds.

(3) The failure of pancreatic enzyme therapy to reverse the hypersecretion suggests that either the duodenum is the major source of non-acid induced inhibition, or pancreatic enzymes do not contribute significantly to it.

Surgical Significance of the Results of Duodenal Transposition

This study was designed to evaluate the role of intestinal factors in gastric secretion. The findings have no immediate surgical importance but do allow some observations on clinical events.

1. Gastro-jejunostomy results in a high incidence of stomal ulceration which has been attributed to loss of neutralizing juice, decreased mucosal resistance and increased acid secretion. This study re-emphasizes the role of increased acid production secondary to loss of duodenal acid inhibition in this type of ulcer.

2. Following gastric resection the Bilroth I or Bilroth II type of anastomosis is favoured by different surgeons. Theoretically, the Bilroth I should be much superior but clinically there is very little difference in the incidence of ulcer. This experiment may in part explain this dichotomy. By doing a Bilroth II type of anastomosis, all one will lose is acid-induced inhibition of duodenal origin. This has been demonstrated to be of much less importance than other intestinal inhibitor mechanisms which would still be operating.

FIGURES

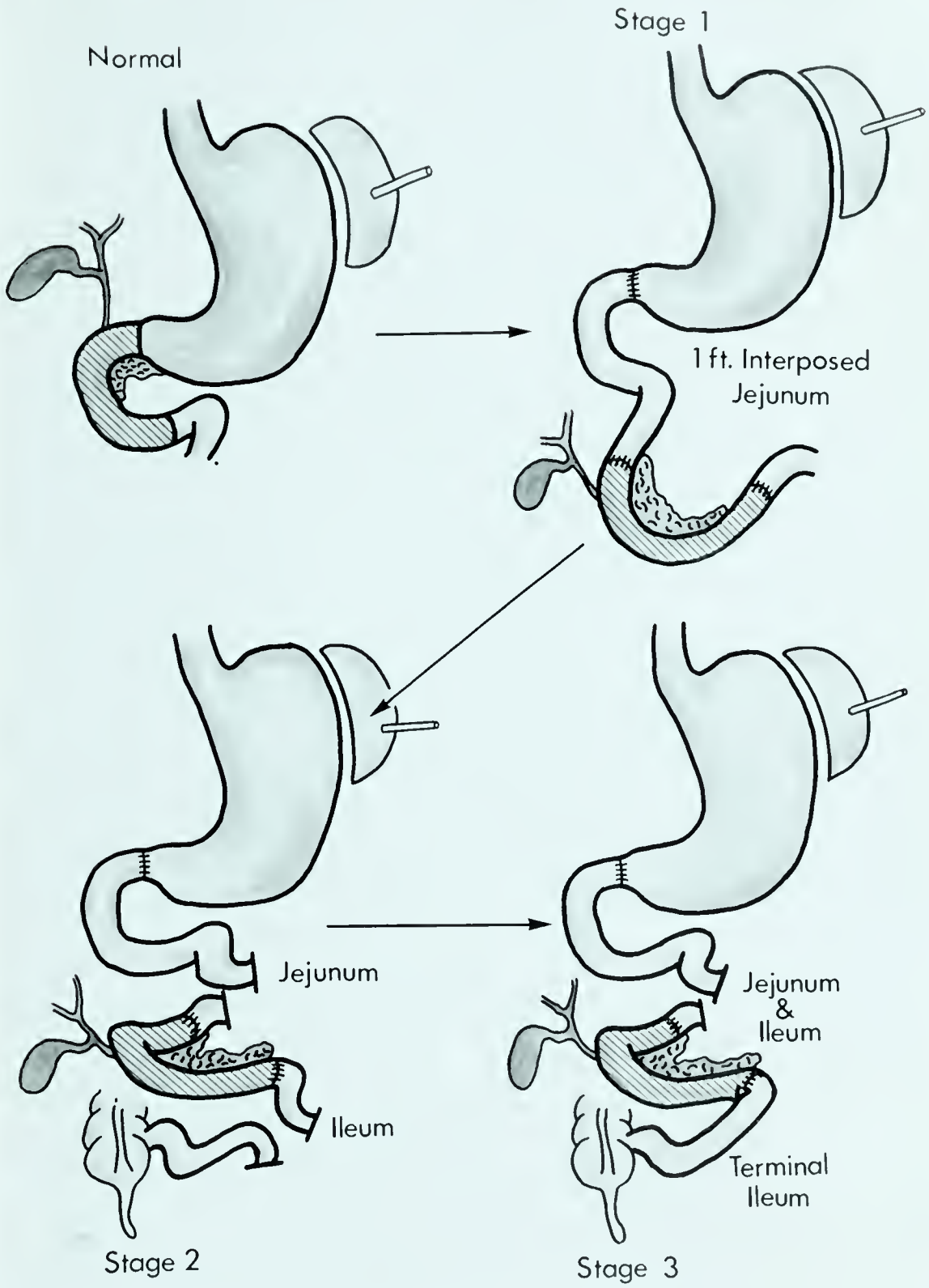


FIGURE I

THE THREE STAGES OF DUODENAL TRANSPOSITION

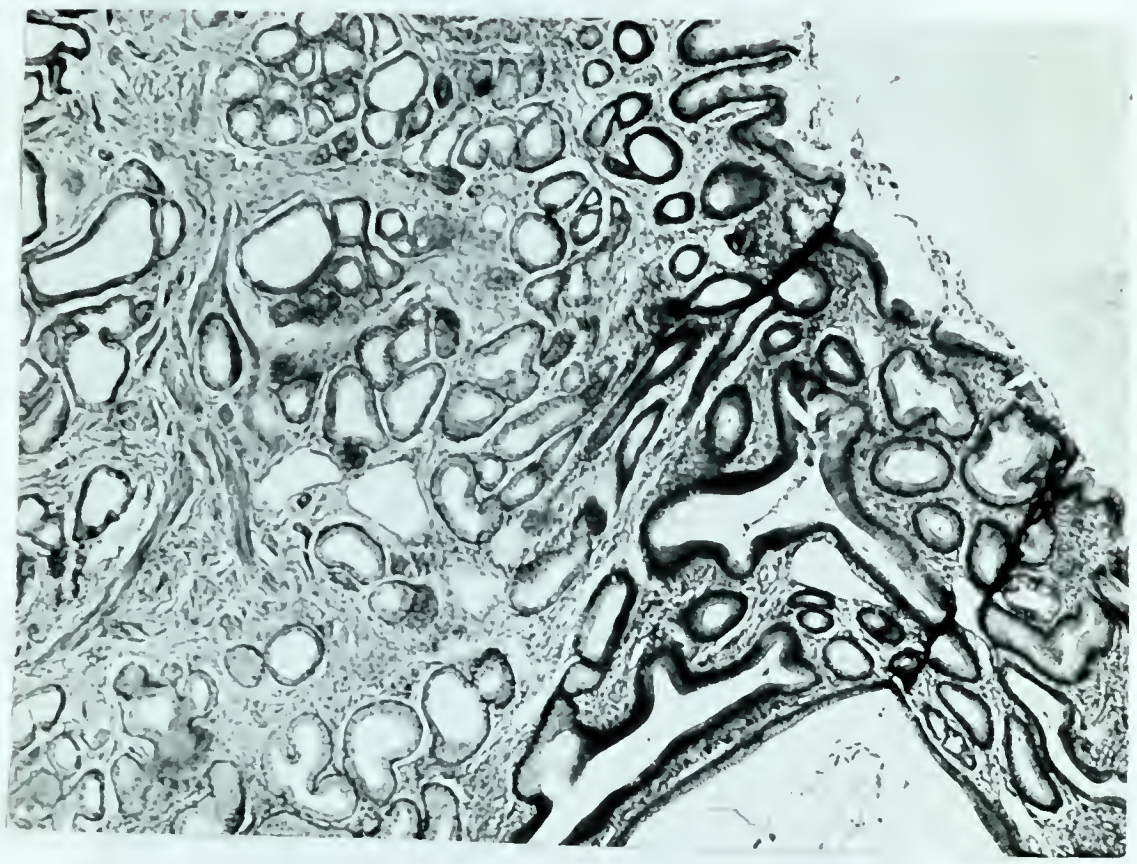
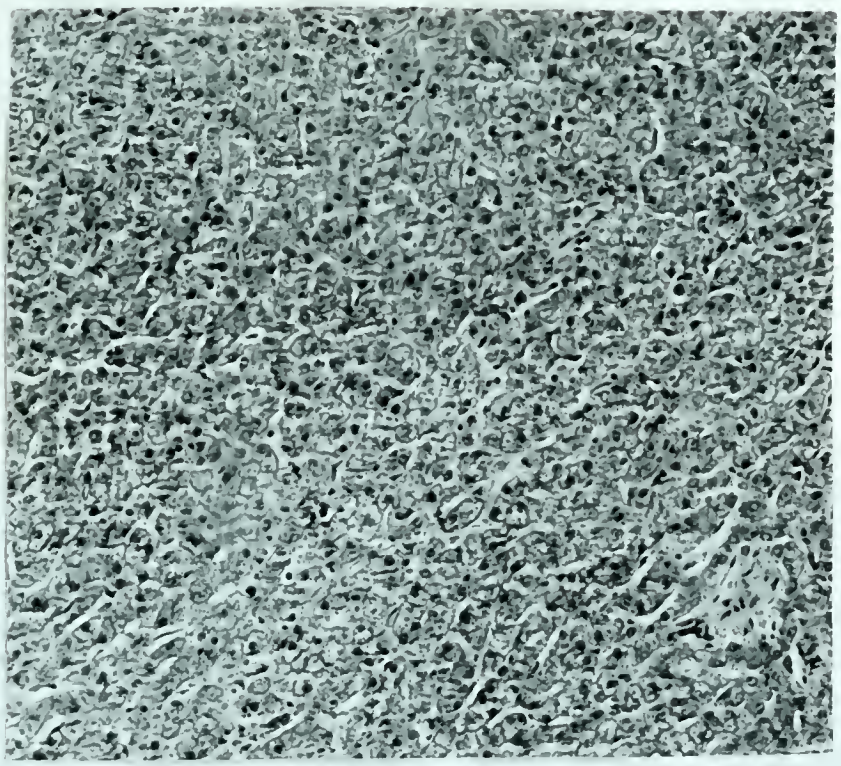


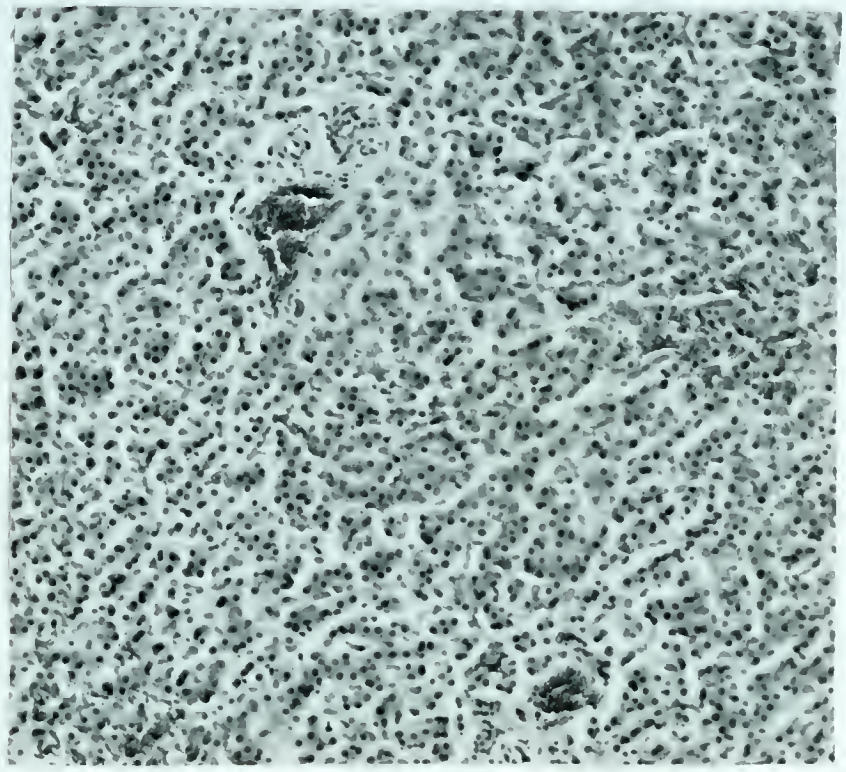
FIGURE 2

Dog #344 - ADENOMATOUS MUCOSAL PROLIFERATION
AT GASTROJEJUNAL ANASTOMOSIS (X25)



3(a) Normal (X150)

Liver biopsy
at Stage III
Surgery



3(b) Atrophy of (X100)

Liver at
autopsy 38
days later

FIGURE 3

Dog #456 - LIVER SECTIONS

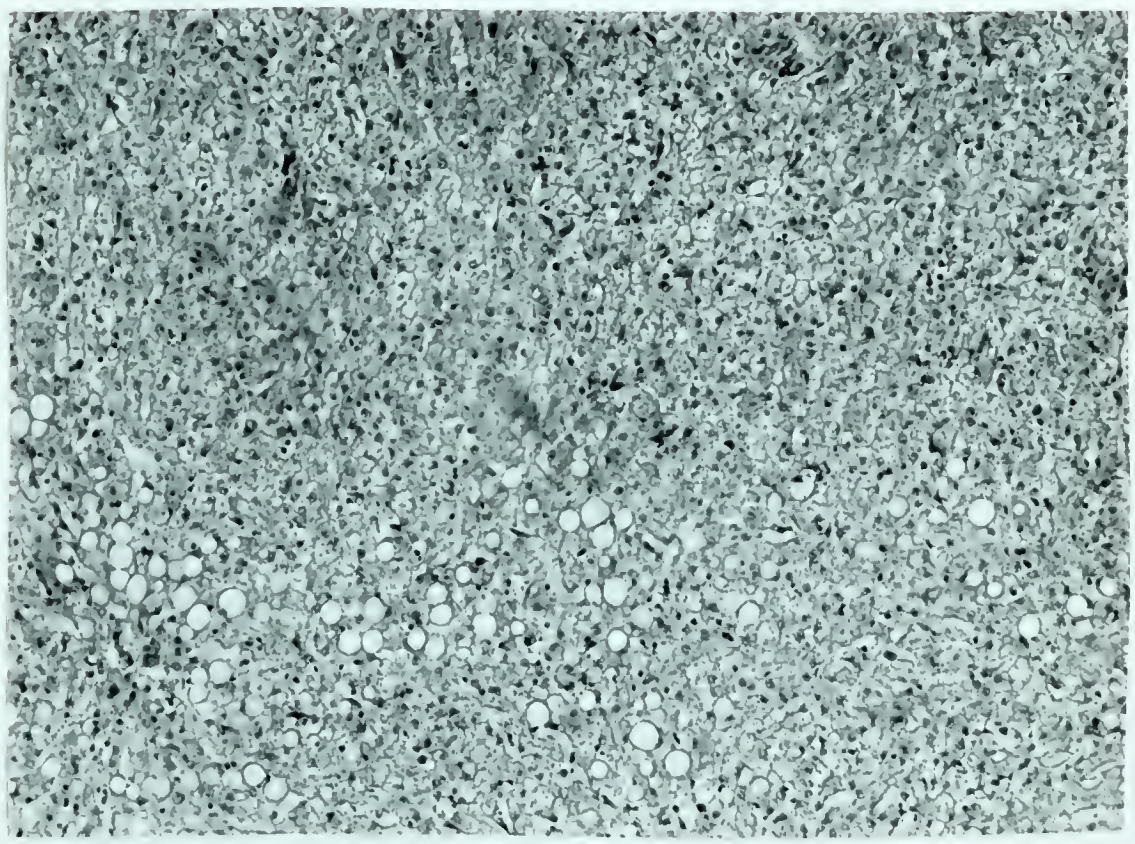


FIGURE 4

Dog #477 - MICROSCOPIC APPEARANCE OF LIVER
AFTER 64 DAYS IN STAGE III
(Fatty Metamorphosis) (X100)

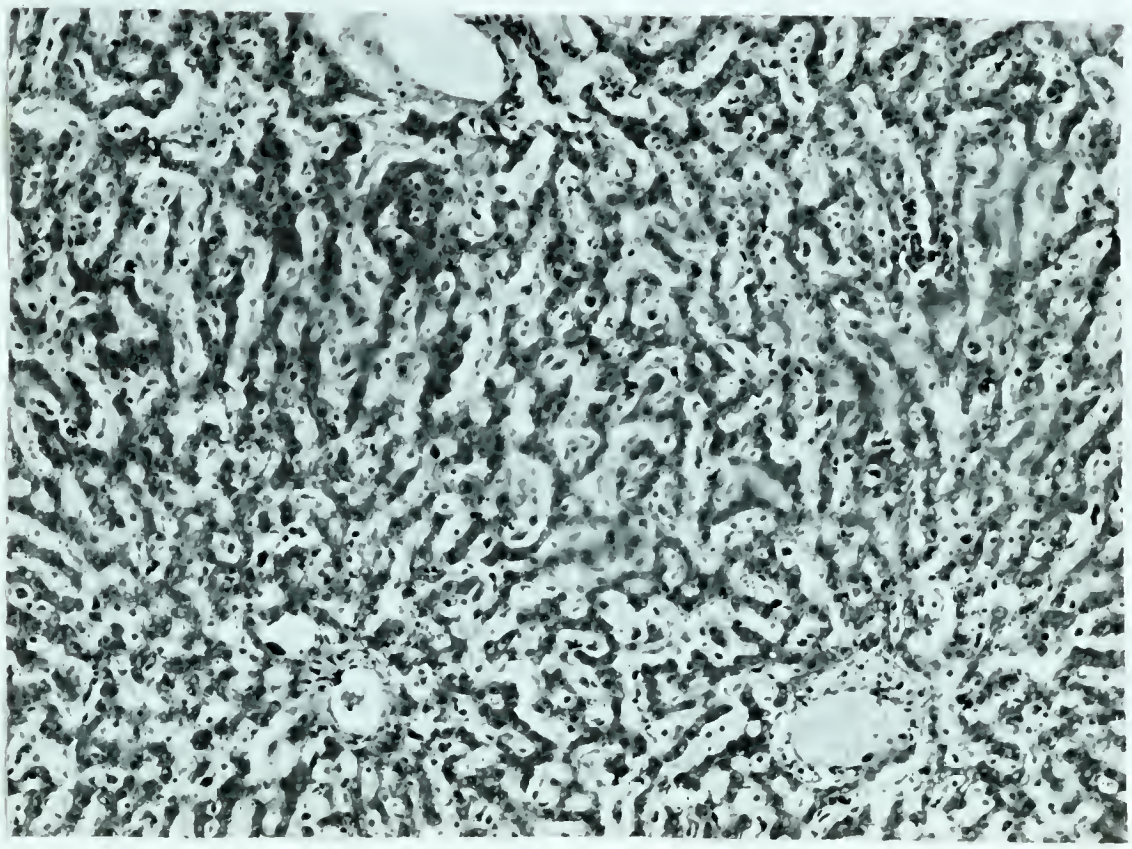


FIGURE 5

Dog #478 - MICROSCOPIC APPEARANCE OF LIVER
AFTER 15 DAYS IN STAGE III Atrophy X150

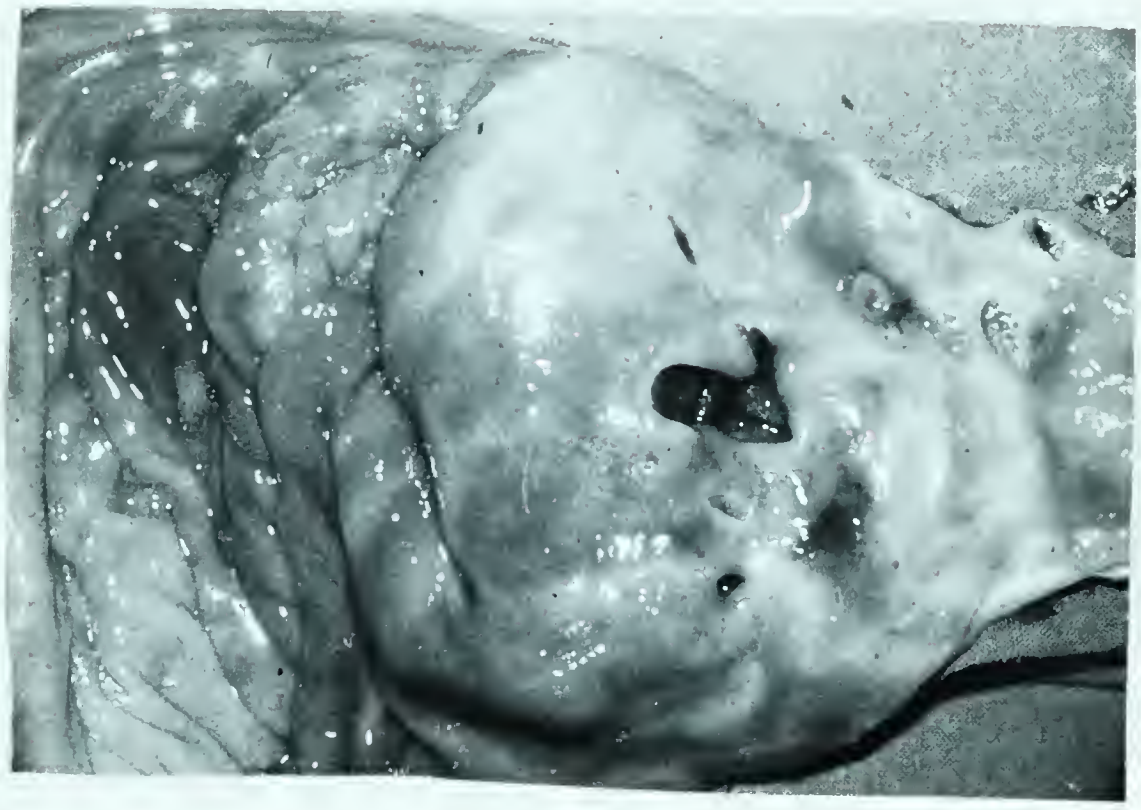


FIGURE 6

Dog #319 - ACUTE ANTRAL ULCERS NOTED AT AUTOPSY
5 DAYS AFTER STAGE III TRANSPOSITION

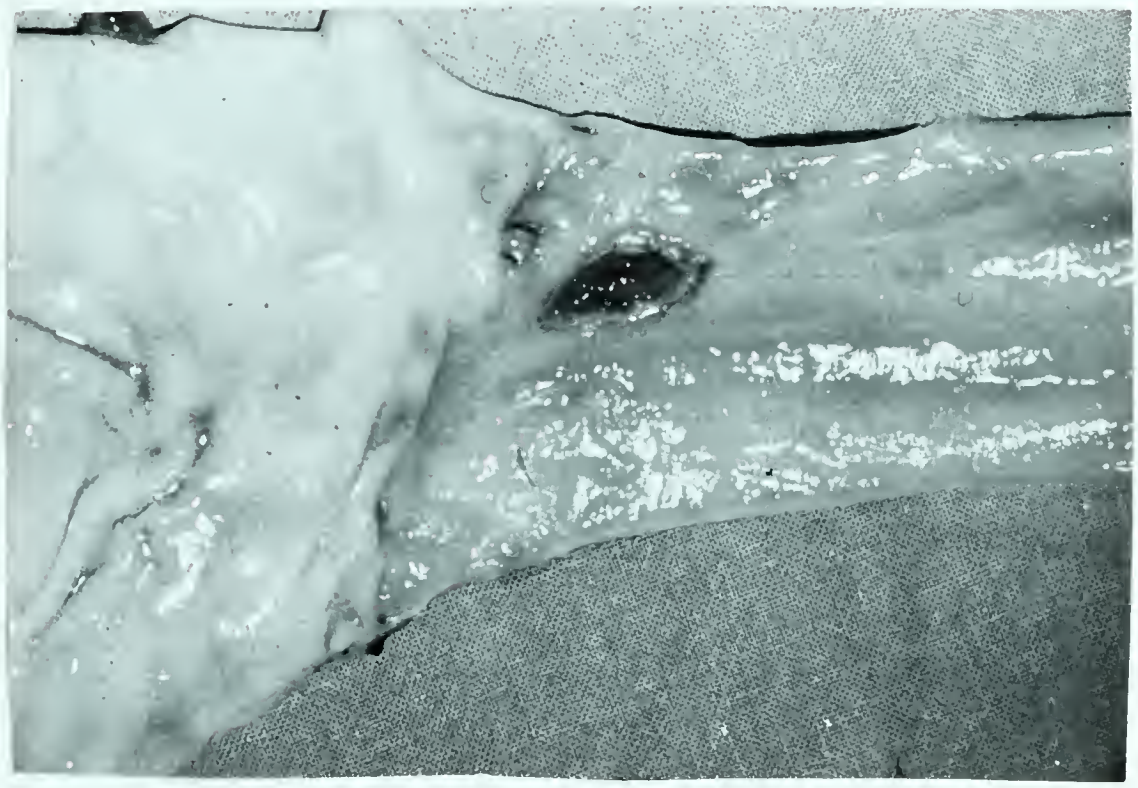


FIGURE 7

Dog #457 - SUBACUTE JEJUNAL ULCER NOTED AT AUTOPSY
21 DAYS AFTER STAGE III TRANSPOSITION

TABLES

TABLE 1

THE EFFECT OF STAGE 1 TRANSPOSITION ON GASTRIC SECRETION

Dog #	Average mEq. HCl Secreted H-Pouch	Stage I	% Change
313	77.82	105.15	+ 35
314	58.48	68.00	+ 16
315	31.28	64.83	+ 107
316*	4.14	6,49	+ 56
317	34.45	53.11	+ 54
319	60.32	56.58	- 6
322	44.96	39.07	- 13
325*	3.63	1.70	- 53
337	21.74	48.28	+ 122
338	21.82	29.51	+ 35
342	31.21	54.21	+ 74
344	44.25	46.25	+ 5
348*	2.92	4.93	+ 69
349	47.69	73.23	+ 53
451	21.15	26.68	+ 26
453	9.40	11.20	+ 19
		Average	+ 38%

P less than 0.05 (sign test)

* 8 hour total post prandial collection. All other collections were 24 hour four meal collections.

TABLE II

THE EFFECT OF STAGE II TRANSPOSITION ON GASTRIC SECRETION

(AS COMPARED TO STAGE I)

	Average mEq. HCl Secreted		
Dog #	Stage I	Stage II	% Change
313	105.15	150.62	+ 43
314	68.00	52.72	- 22
315	64.82	98.95	+ 52
316*	6.49	9.93	+ 34
319	56.58	122.40	+ 116
322	39.07	79.88	+ 104
325+	1.70	3.48	+ 105
337	48.28	53.40	+ 10
338	29.51	42.54	+ 45
342	54.21	59.58	+ 10
344	46.25	62.86	+ 36
348*	4.92	19.68	+ 293
453	11.20	24.25	+ 116
		Average	+ 73%
		P = 0.01 (sign test)	

* 8 hour total post prandial collection. All other collections were 24 hour four meal collections.

TABLE III

THE EFFECT OF STAGE II TRANSPOSITION ON GASTRIC SECRETION

(AS COMPARED TO H-POUCH)

Dog #	Average mEq. HCl Secreted H-Pouch	Stage II	% Change
313	77.82	150.62	+ 94
314	58.48	52.72	- 10
315	31.28	98.95	+ 218
316*	4.15	9.93	+ 139
319	60.32	122.40	+ 103
322	44.96	79.89	+ 78
325*	3.63	3.45	- 4
337	21.74	53.40	+ 146
338	21.82	42.54	+ 95
342	31.21	59.59	+ 91
344	44.25	62.86	+ 42
348*	2.92	19.68	+ 573
453	9.40	24.25	+ 158
		Average	+ 133%

P less than 0.05 (sign test)

* 8 hour total post prandial collection. All other collections were 24 hour four meal collections.

TABLE IV

THE EFFECT OF STAGE III TRANSPOSITION ON GASTRIC SECRETION

(AS COMPARED TO H-POUCH)

Dog #	Average mEq. HCl Secreted H-Pouch	Stage III	Distance to I.C. Valve (inches)	% Change
316*	4.15	9.36	24	+ 126
455*	3.65	10.23	27	+ 182
461	29.80	51.94	15	+ 74
462	26.21	94.30	29	+ 221
			Average	+ 151%

* 8 hour total post prandial collection. All other collections were 24 hour four meal collections.

TABLE V

THE EFFECT OF STAGE III DUODENAL TRANSPOSITION ON GASTRIC SECRETION

(AS COMPARED TO STAGE II)

Dog #	Average mEq. HCl Secreted H-Pouch	Stage III	Distance to I.C. Valve (inches)	% Change
316*	9.93	9.36	24	- 6
467**	3.07	10.05	14	+ 226
477**	15.24	12.48	20	- 18[1]
478**	11.98	22.51	19	+ 88[1]
			Average	+ 72%

* 8 hour total post prandial collection

** 6 hour total post prandial collection

[1] microscopic evidence of liver disease at autopsy.

TABLE VI

GASTRIC SECRETION AFTER SUCCESSIVE DUODENAL TRANSPOSITION TO THE STAGE I, II AND III POSITIONS

	Average Percentage Change in Gastric Secretion		
	When Compared to H-Pouch	When Compared to Stage I	When Compared to Stage II
Stage I	+ 38% (16)*		
Stage II	+ 133% (13)	+ 73% (13)	
Stage III	+ 151% (4)		+ 72%** (4)

* Number in brackets indicates number of dogs on which average is based.

** Only 2 of the 4 dogs demonstrated an increase.

TABLE VII

THE EFFECT OF REVERTING A TRANSPOSED DUODENUM TO A MORE PROXIMAL POSITION

	mEq. Free HCl Secreted		
Dog #	Duodenum in a Distal Position	After Moving Duodenum Proximally	% Change
451	26.67 (Stage I)	13.51 (H-Pouch)	- 49.3
481	16.87 (Stage II)	9.30 (Stage I)	- 44.9
482	23.50 (Stage II)	23.10 (Stage I)	0
461	52.34 (Stage III)	23.21 (Stage I)	- 55.7

The position of the duodenum is indicated in the brackets.

TABLE VIII

HOUR OF MAXIMUM ACID SECRETION BEFORE AND AFTER DUODENAL TRANSPOSITION TO THE TERMINAL ILEUM

Dog #	Hour of Maximum Acid Secretion Before Transposition	After Transpos.
455	5	3
456	3	2
457	4	6
461	1	1
462	6	2

TABLE IX

HOUR AT WHICH ACID SECRETION FELL TO 10%
OF THE MAXIMAL ACID SECRETION.

A COMPARISON BEFORE AND AFTER DUODENAL TRANSPOSITION
TO THE TERMINAL ILEUM

Dog #	Hour at Which 10% of Maximal Response Was Reached	
	Before Transposition	After Transposition
455	9	15
456	11	9
457	14	12
461	9	7
462	7	20

TABLE X

THE EFFECT OF TRANSPOSING THE DUODENUM TO THE TERMINAL ILEUM ON THE EARLY AND LATE POST PRANDIAL SECRETION

	% Change in Gastric Secretion After Transposition			
	Antral** Phase	Antral & Early** Intestinal Phase	Intestinal** Phase	Fasting** Phase
455	+ 195	+ 156	+ 578	+ 10714
456	+ 104	+ 83	+ 22	- 39
457	- 46	- 43	+ 117	- 12790
461	+ 150	+ 85	+ 235	+ 87
462	+ 838	+ 648	+1339	+++*
Average Increase	+ 257	+ 186	+ 458	+++

** These terms are approximations of the stimulus provided to the stomach at the time of collection. They stand for the following:

"Antral Phase" - total secretion collected in first four hours after a meat gruel meal.

"Antral and Early Intestinal Phase" - total secretion collected in hour 5 to hour 8 following a meat gruel meal.

"Intestinal Phase" - total secretion collected in hours 9 - 16 following a meat gruel meal.

"Fasting Phase" - total secretion collected in hours 17 - 24 following a meat gruel meal.

* As an Heidenhain pouch preparation, no fasting collections were measurable in terms of acidity in this dog due to insufficient volume.

TABLE XI

THE EFFECT OF PREDIGESTION OF DIET WITH VIOKASE ON GASTRIC SECRETION

Dog #	Average mEq. HCl Secreted in 24 hours			
	Standard Diet	Incubation Alone	Incubation with Viokase	% Change After Viokase Addition
H-Pouch Preparations				
464	55.852 (36)*	52.956 (8)	71.515 (60)	+ 28
465	53.599 (24)	48.392 (7)	69.119 (55)	+ 29
Stage III Preparations				
461	51.940 (13)	not done	51.428 (58)	0
462	94.302 (12)	not done	107.161 (15)	+ 8.7

* Numbers in brackets indicate number of collections on which average is based.

TABLE XII

BSP RETENTION IN NORMALS AND AFTER DUODENAL TRANSPOSITION

Normals			
	Number of Determinations	18	
	Average Value	12.34%	
	Range	11.61% - 13.05%	
		Within 30 days of Surgery	Over 30 days Since Surgery
Stage I	Number of Determinations	2	13
	Average Value (%)	12.23	12.37
	Range (%)	11.51 - 12.94	9.97 - 13.00
Stage II	Number of Determinations	7	8
	Average Value (%)	12.63	12.84
	Range (%)	11.52 - 12.94	12.73 - 12.99
Stage III	Number of Determinations	10	12
	Average Value	12.54	12.77
	Range	11.84 - 12.94	11.92 - 13.07

TABLE XIII

SERUM ALKALINE PHOSPHATASE IN NORMALS AND AFTER DUODENAL TRANSPOSITION

Normals		Non-Operated	H - Pouch
	Number of Determinations	6	50
	Average Value	1.45	1.21
	Range	0.37 - 1.99	0.28 - 2.28
		Within 30 days of Surgery	Over 30 days Since Surgery
Stage I	Number of Determinations	7	12
	Average Value	1.35	1.19
	Range	0.61 - 2.11	0.35 - 2.03
Stage II	Number of Determinations	8	8
	Average Value	1.66	1.56
	Range	0.85 - 3.17	0.70 - 3.88
Stage III	Number of Determinations	8	4
	Average Value	1.53	1.26
	Range	0.68 - 3.50	0.61 - 2.03

TABLE XIV

SERUM AMYLASE IN NORMALS AND AFTER DUODENAL TRANSPOSITION

Normals			
	Number of Determinations	49	
	Average Value	110.7	
	Range	42 - 144	
		Within 30 days of Surgery	Over 30 days Since Surgery
Stage I	Number of Determinations	6	10
	Average Value	71.6	122
	Range	48 - 90	60 - 240
Stage II	Number of Determinations	4	9
	Average Value	113.5	81.1
	Range	72 - 180	36 - 144
Stage III	Number of Determinations	9	3
	Average Value	66	78.3
	Range	48 - 90	34 - 129

TABLE XV

PLASMA HISTAMINES

	No. of Determinations	Average	Range	Median
FASTING				
Normals	4	0.1357	0.1152 - 0.1700	0.1335
Stage II	3	0.1213	0.0978 - 0.1384	0.1282
Stage III	3	0.1000	0.0948 - 0.1082	0.0972
3-HR. POST PRANDIAL STUDIES				
Normals	6	0.1603	0.1142 - 0.2016	0.1603
Stage I	1	0.1094	-	-
Stage II	6	0.1278	0.0953 - 0.1448	0.1221
Stage III	5	0.0984	0.0675 - 0.1316	0.0909

TABLE XVI

THE EFFECT OF H-POUCH CONSTRUCTION AND DUODENAL TRANSPOSITION ON BODY WEIGHT

	No. of Dogs	Average No. of Days Studied	Average % Wt. Change	Average Wt. Loss per Wk.
H-Pouch	26	96.1	- 13.2%	- 1.07%
Stage I	16	75.4	+ 0.31%	0
Stage II	13	60.5	- 9.9%	- 1.1%
Stage III	12	44	- 28%	- 4.5

TABLE XVII

THE EFFECT OF PREDIGESTION WITH VIOKASE ON NUTRITION AS MANIFESTED BY WEIGHT

Dog #	Original Weight (kg)	Weight prior to food pre-digestion (kg)	No. of Days Fed	Weight after feeding of predigested food	% Change
I. In Normal Dogs (H-Pouch					
464	29	27	72	30	+ 11%
465	21	19	72	22	+ 16%
II. In Dogs With a Pancreatic Fistula (Stage III)					
461	24	17	62	20.5	+ 21%
462	21	13	16	14*	+ 8%

* This dog suffered from an erosion about the cannula with eventual leak into the peritoneal cavity and death. He ate poorly throughout the period of viokase feeding.

TABLE XVIII

LIVER DISEASE

Dog #	Stage	Survival Time (Days)	Distance to I.C. Valve (inches)	Gastric Secretion Studies	Cause of Death	Microscopic Appearance of Liver
456	III	38	18	not acceptable	Perforated ulcer (2 antral, 1 jejunal)	Atrophy of Liver cells (Figure 3)
477	III	64	20	18% fall from Stage II levels	Sacrificed at completion of Study	fatty Metamorphosis (Figure 4)
478	III	15	19	88% increase over Stage II Levels	Sacrificed for Inanition	Atrophy of Liver cells (Figure 5)

TABLE XIX

PEPTIC ULCERATION

Dog #	Stage	Survival Time (Days)	Distance to I.C. Valve (inches)	Gastric Secretion Studies	Cause of Death	Findings at Autopsy
319	III	5	14	not studied in III. 122% increase over H-pouch levels while in Stage II	Perforated antral ulcer	5 acute antral ulcers (Figure 6)
337	II	90	72	146% increase over H-pouch levels	Perforated jejunal ulcer	5 subacute jejunal ulcers
456	III	38	18	not acceptable	Perforated antral ulcer	- Subacute ulcers, 2 antral, 1 jejunal. - Numerous gastric petechiae - hepatic cellular atrophy (Figure 3)
457	III	21	23	not acceptable	Perforated jejunal ulcer	Subacute jejunal ulcer (Figure 7)

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